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[Original Article]

Attempting to define sentinel node micrometastasis in oral squamous cell carcinoma

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Abstract

OBJECTIVE : The aim of this supplemental study of a sentinel node (SN) biopsy (SNB) trial for oral squamous cell carcinoma (OSCC) was to assess the effectiveness in identifying micrometastasis and determining whether elective neck dissection (END) is necessary.

MATERIALS AND METHODS : Twenty-three patients with pathologically positive SNs were included. The sizes of the metastatic lesions in positive SNs (SMSNs) were classified and the rates of occult metastasis of non-SNs were compared.

RESULTS : The patients were divided according to the SMSN : <0.2 mm (group A, $n=3$) ; 0.2 mm to <2.0 mm (group B, $n=7$) ; and ≥ 2.0 mm (group C, $n=13$). The rates of occult metastasis in groups A, B, and C were 0% (0/3), 14% (1/7) and 23% (3/13), respectively.

CONCLUSION : Rare cancer cell distribution to nodes other than SNs was observed in the patients with SN metastatic lesions of at least smaller than 0.2 mm in size, suggesting the possibility of defining SN micrometastasis in N0 OSCC.

Key words : sentinel node, oral squamous cell carcinoma, micrometastasis.

Introduction

Elective neck dissection (END) is recommended for N0 oral squamous cell carcinoma (OSCC) patients ; however, it often causes severe complications. To avoid any unnecessary END, sentinel node (SN) biopsy (SNB) for OSCC, which has been clinically used in Western countries, will soon be ad-

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opted in Japan to assess the presence of metastasis. Although there are various phases of lymph node metastasis, from micrometastasis to fully occupied [1], there is no concern about the definition of micrometastasis in the current TNM system for OSCC. For breast cancer, however, it is common to further differentiate micrometastasis from macrometastasis and treat the conditions differently. However, for OSCC, if the sentinel node is pathologically positive, neck dissection should be performed. The aim of the present study was to assess the effectiveness of SNB in identifying micrometastasis and determining whether END is necessary for patients with OSCC. The present investigation is an original and unique attempt to clarify the perspectives to define non-invasive treatment for micrometastasis of OSCC and define the novel concept of SNB for OSCC.

Materials

We analyzed the association between treatment outcomes and the size of metastatic lesions in the SN among patients enrolled in a prospective multicenter phase II SNB trial titled 'UMIN000004951 ; Evaluation of selective neck dissections based on sentinel lymph node navigation in oral cancers'[2]. Patients who were managed at 10 institutions, with previously untreated N0 OSCC (n=57) with a clinical tumor stage of "late-T2" (T2 tumor with a diameter of ≥3 cm or any T2 tumor with a tumor depth of ≥5 mm) or T3 were included in the present study.

Preoperatively, the SNs were localized using conventional lymphoscintigraphy : At 24 h before surgery, technetium 99 m (99mTc) phytate (FUJIFILM RI Pharma Co., Ltd. and Nihon Medi-Physics Co., Ltd., Japan), which was used as a radiotracer, was injected submucosally (74 MBq in 1 mL) at four points (one point in each quadrant) around the primary tumor, and lymphoscintigraphy was performed to map the SNs. During surgery, tumor resection was performed, followed by the detection of SNs with a handheld gamma probe, and selective ND with SN basin dissection. The SNs were immediately submitted for a frozen section pathological analysis, then ranked according to their tracer uptake level, which was up to 5. All SNs were cut into 2-mm blocks, and were subjected to an intraoperative frozen section analysis. SNs in which a cancer lesion was pathologically detectable were defined as positive SNs, those in which a cancer lesion was not pathologically detectable were defined as negative SNs. In patients with positive SNs, therapeutic ND of levels I, II, III, and IV was performed, whereas ipsilateral prophylactic ND of levels I, II, and III was performed for patients with negative-SNs, in a one-stage procedure. Additional sections were stained with hematoxylin and eosin (HE) and AE1/3 cytokeratin (Signet Laboratories, MA, USA) to determine the final postoperative diagnosis. All other lymph nodes, including non-radioactive lymph nodes, were considered to be non-sentinel nodes (NSNs). NSNs were divided longitudinally into two specimens, and a single representative cross-section was stained with HE to determine the final postoperative diagnosis. The details of the clinical methods and modifications are described in our previous paper[2].

Methods

Occult metastasis of NSN was defined as the presence of cancer cells within NSNs (positive NSNs) in the level of therapeutic ND at surgery and of post-operative node metastasis (PONM) without primary recurrence during the follow-up period.

The sizes of the metastatic lesions in positive SNs (SMSNs) based on AE1/3 cytokeratin staining were classified into three groups according to the AJCC 6th edition for breast cancer[3] : isolated tumor cells (ITC, group A : single cells or clusters of cells of <0.2 mm in diameter) ; micrometastasis (group B : 0.2 mm to <2.0 mm in diameter) ; and macrometastasis (group C : ≥2 mm in diameter). The rates of occult metastasis of NSNs and survival rates were compared among the groups. When multiple metastatic lesions existed within one lymph node, the lesion of the greatest dimension was measured.

Results

The patient characteristics are listed in Table 1. Twenty-three patients with metastasis-positive SNs were divided into three groups according to the diameter of the metastatic lesions in the SNs. Groups A, B and C consisted of 3, 7, and 13 patients, respectively. The rates of postoperative node metastasis in groups A, B, and C were 0% (0/3), 14% (n=1/7), and 8% (1/13), respectively. In group C, one patient had positive NSNs and developed PONM. Thus, the rates of occult metastasis in groups A, B, and C were 0% (0/3), 14% (1/7) and 23% (3/13), respectively. Although there was no significant difference, the 3-year overall survival rates of all cases, groups A, B, and C were 83%, 100%, 57%, 83%, and the 3-year disease-free survival rates of all cases, groups A, B, and C were

Table 1. Patient characteristics.

Characteristic	Positive SN	Negative SN	Total	
Number	23	34	57	
Age, median (range), years	62 (30–77)	66 (30–85)	64 (30–85)	
Male	18	24	42	N/S
Female	5	10	15	
Tumor location				N/S
Tongue	22	27	49	
Floor of the mouth	1	3	4	
Alveolar ridge	0	3	3	
Buccal mucosa	0	1	1	
T stage				N/S
late T2	20	30	50	
T3	3	4	7	
Tumor resection method				N/S
Trans oral	14	26	40	
Pull-through	9	8	17	
Reconstruction method				N/S
Pedicle-flap	2	5	7	
Free-flap	5	8	13	
Node dissection				N/S
Ipsilateral	18	30	48	
Bilateral	5	4	9	
NSN	3	2	5	N/S
PONM	2	1	3	N/S

SN : sentinel node, NSN : non-sentinel node, PONM : post-operative node metastasis

Table 2. Rate of occult metastasis in each group

Group	SMSN	*n*	Positive NSN	PONM	Rate of occult metastasis
A	0.2 mm>	3	0	0	0% (0/3)
B	=<0.2 mm, 2.0 mm>	7	0	1	14% (1/7)
C	=<2.0 mm	13	3	1*	23% (3/13)
Total		23	3	2*	17% (4/23)

SMSN : size of metastatic lesion in positive sentinel node, NSN : non-sentinel node,
PONM : post-operative node metastasis, *A case had both positive NSN and PONM.

74%, 100%, 77%, 74%, respectively.

Discussion

Lymph node metastasis is an important factor in the prognosis of OSCC. In the management of the neck for early OSCC, the 'wait and see' policy is not recommended, because both the local control rate and survival of patients with lymph node metastasis have been reported to be less than half in comparison to patients without lymph node metastasis[4,5] and it is strongly suggested that END should be routinely performed[6-8]. The purpose of SNB for OSCC is to distinguish cases where metastasis is not detected in the SN and in which END is avoidable[9]. SNB is also reported to be associated with significantly higher postoperative mobility and a better shoulder function in comparison to END[10]. SNB is useful not only as an accurate diagnostic tool for detecting lymph node metastasis, but also as a tool for prognostic stratification in various fields of cancer[11-13]. SNB for OSCC is still in the clinical research stage in Japan, but it has been established as a standard treatment in Europe[14] and the United States[15], and its consensus has already been reached all over the world[16].

In the treatment of breast cancer, micrometastasis is considered an important factor for predicting the prognosis and selecting surgery[17,18]. Although a patient with either macrometastasis or microme-

tastasis is considered pathologically positive for lymph node metastasis, ITCs are classified as node-negative and its prognostic impact was reported to be weak[19,20]. SN selective dissection is sufficient for obtaining regional and distant control in patients with early-stage breast cancer and micrometastasis in the SN[21].

The current concept of the sentinel node navigation surgery (SNNS) for OSCC is that therapeutic neck dissection should be performed for SN-positive cases, and that END is unnecessary for SN-negative cases. Although SNB for OSCC has been clinically used in Western countries, and a multi-institutional study of SNB for head and neck cancer has also been undertaken in Japan[2,22], the spread of the concept of SNB for OSCC is still insufficient. One of the reasons might be the aggressiveness of this concept. To define the micrometetastasis for OSCC and discover the possibility of the low invasive treatment for micrometastasis would be necessary. The present investigation would be an original and unique attempt to clarify these perspectives.

Occult metastasis did not occur in patients whose SMSNs were smaller than 0.2 mm. In other words, no cancer cell distribution to nodes other than SNs was observed in patients with SN metastatic lesions at least smaller than 0.2 mm, suggesting the possibility to define the micrometastasis for determination whether END is necessary for patients with OSCC.

A limitation of the present study is its relatively small sample size. This analysis was conducted using the available data of 57 patients in a phase II study. A further, larger scale study to establish the cutoff value for micrometastasis and to develop an individualized, minimally invasive approach is necessary.

Conclusion

No cancer cell distribution to nodes other than SNs was observed in patients with SN metastatic lesions at least smaller than 0.2 mm, suggesting the possibility to determine whether END is necessary for patients with OSCC.

Conflict of Interest

The authors declare that they have no conflicts of interest associated with this manuscript.

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